Citation:

Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: Evaluating the risks and the benefits. *JAMA.* 2006 Oct 18; 296(15): 1,885-1,899.

PubMed ID: 17047219

Study Design:

Meta-analysis or Systematic Review

Class:

M - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

- To elucidate the relative risks and benefits
- This study reviewed the scientific evidence for adverse and beneficial health effects of fish consumption.

Inclusion Criteria:

- Articles published through April 2006 that were identified through MEDLINE, governmental reports, systematic reviews and meta-analyses and that evaluated:
  - Intake of fish or fish oil and cardiovascular risk
  - Effects of methylmercury and fish oil on early neurodevelopment
  - Risks of methylmercury for cardiovascular and neurologic outcomes in adults
  - Health risks of dioxins and polychlorinated biphenyls in fish
- Studies primarily evaluating risk in humans and focusing on evidence, when available, from randomized trials and large prospective studies
- MEDLINE reports only in English language, only involving studies in humans, and adult or child populations (as appropriate)
- Reports identified via searches of related articles of relevant identified manuscripts as well as by hand reviews of references from identified reports and direct contact with investigators.

Exclusion Criteria:

- Articles published after April 2006
- Articles that evaluated subjects other than:
  - Intake of fish or fish oil and cardiovascular risk
  - Effects of methylmercury and fish oil on early neurodevelopment
  - Risks of methylmercury for cardiovascular and neurologic outcomes in adults
  - Health risks of dioxins and polychlorinated biphenyls in fish

- Articles examining other potential benefits of fish intake (e.g., for cognitive decline or dementia, depression or neuropsychiatric disorders and asthma or inflammatory disorders)
- Studies that did not primarily evaluate risk in humans or focus on evidence, when available, from randomized trials and large prospective studies
- MEDLINE reports in foreign languages other than English, and involving studies in animals.

Description of Study Protocol:

Recruitment

- Articles published through April 2006 were identified through MEDLINE, governmental reports, systematic reviews and meta-analyses, and included studies primarily evaluating risk in humans and focusing on evidence, when available, from randomized trials and large prospective studies. Reports were identified via searches of related articles of relevant identified manuscripts as well as by hand reviews of references from identified reports and direct contact with investigators
- MEDLINE search terms: (Fish or n-3 PUFA or omega-3) and (coronary or cardiac or cardiovascular or mortality) and (clinical trial or prospective or meta-analysis); (fish or n-3 PUFA or omega-3 or docosahexaenoic or mercury or methylmercury) and (cognitive or neurologic or neurodevelopment) and (clinical trial or prospective or meta-analysis); (mercury or methylmercury) and (coronary or cardiac or cardiovascular or cognition or neurologic) and (clinical trial or prospective or meta-analysis); (dioxin or polychlorinated biphenyl or PCB) and (fish or seafood)
- One author screened all identified studies, and the final articles included were selected by both authors by consensus
- Metabolic studies and animal-experimental evidence were also considered to elucidate potential mechanisms of effect.

Design

Systematic review.

Statistical Analysis

- The evidence for risks and benefits was considered overall and among different at-risk populations. When possible, pooled or meta-analyses were performed to characterize effects most precisely
- The relationship between intake of fish or fish oil and relative risk of coronary heart disease (CHD) death in a pooled analysis of the prospective studies and randomized trials was evaluated non-parametrically
- Relative risks (RR) in the control and intervention groups (for randomized trials) or RR in the reference group and multi-variable-adjusted relative risks in the comparison groups (for cohort studies) were examined
- In reviewing the risk of total mortality due to intake of fish or fish oil in randomized clinical trials, they examined each trial's contribution (inverse-variance weight) to the pooled estimate (dotted line) and 95% confidence interval, determined by random effects meta-analysis
- Authors noted that because fish intake is related to exposure to many different compounds, including n-3 PUFAs, mercury and PCBs and dioxins, as well as to multiple different health outcomes, including cardiovascular diseases, neurologic outcomes and cancer, a systematic

quantitative review of every possible combination was beyond the constraints of this report.

Data Collection Summary:

- Information on certain study characteristics collected not explicitly described in article for all focused questions (e.g., such as study year of all articles examined, study country of origin of all articles examined, number of subjects per study, treatment timing, duration, dose and outcome assessment timing and method)
- Outcomes collected include:
  - Effect of intake of fish or fish oil on cardiovascular risk
  - Effects of methylmercury and fish oil on early neurodevelopment
  - Risks of methylmercury for cardiovascular and neurologic outcomes in adults
  - Health risks of dioxins and polychlorinated biphenyls in fish.

Description of Actual Data Sample:

- *Age:* Examined outcomes in adult men and women, pregnant women and children including infants
- *Location:* European, Japanese, and United States of America.

Summary of Results:

Overall Findings

- Modest consumption of fish (e.g., one to two servings per week), especially species higher in the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), reduces risk of coronary death by 36% (95% CI: 20% to 50%; P<0.001) and total mortality by 17% (95% CI: 0% to 32%; P=0.046) and may favorably affect other clinical outcomes
- Intake of 250mg per day of EPA and DHA appears sufficient for primary prevention
- DHA appears beneficial for, and low-level methylmercury may adversely affect, early neurodevelopment
- Health effects of low-level methylmercury in adults are not clearly established; methylmercury may modestly decrease the cardiovascular benefits of fish intake.

Specific Findings

- Benefits of fish intake:
  - Cardiovascular outcomes:
    - Evidence from prospective studies and randomized trials reviewed suggests that consumption of fish or fish oil lowers risk of CHD death and sudden death
    - Across different studies, compared with little or no intake, modest consumption (approximately 250 to 500mg per day of EPA and DHA) lowers RR by 25% or more. Higher intakes do not substantially further lower CHD mortality, suggesting a threshold of effect. Pooling all studies, this pattern was clearly evident
    - At intakes up to 250mg per day, the RR of CHD death was 14.6% lower (95% CI: 8% to 21%) per each 100mg per day of EPA and DHA, for a total risk reduction of 36% (95% CI: 20% to 50%). At higher intakes, little additional risk reduction was present (0.0% change per each 100mg per day; 95% CI: −0.9% to

+0.8%)
        - Absolute CHD mortality rates vary more than 100-fold across different populations (due to differences in age, prior CHD and other risk factors), but the relative effects of intake of fish or fish oil are consistent, whether for primary or secondary prevention, for cohort studies or randomized trials or for comparing populations at higher or lower absolute risk
        - Compared with little or no intake, modest consumption (approximately 250 to 500mg per day EPA + DHA) is associated with lower risk of CHD death, while at higher levels of intake, rates of CHD death are already low and are not substantially further reduced by greater intake
        - Comparing different types of fish, lower risk appears more strongly related to intake of oily fish (e.g., salmon, herring, sardines), rather than lean fish (e.g., cod, catfish, halibut)
        - Fish intake may modestly affect other cardiovascular outcomes, but evidence is not as robust as for CHD death
        - The heterogeneity of the effects of fish or fish oil intake on cardiovascular outcomes is likely related to varying dose and time responses of effects on the risk factors
    - Total mortality
        - n-3 PUFAs most strongly affect CHD death and are unlikely to affect appreciably other causes of mortality
        - Authors suggest that given approximately 36% reduction in CHD death, intake of fish or fish oil would reduce total mortality by between approximately 9% (36% reduction by 25% CHD deaths) to approximately 18% (36% reduction by 50% CHD deaths), or an average of approximately 14% in mixed populations
        - When the authors added additional placebo-controlled, double-blind, randomized trials performed since 2003, marine n-3 PUFAs reduced total mortality by 17% (pooled relative risk, 0.83; 95% CI: 0.68 to 1.00; P=.046); and they compared this to effects of statins on total mortality (a 15% reduction) in a meta-analysis of randomized trials (pooled RR, 0.85; 95% CI: 0.79 to 0.92)
    - Neurologic development: Observational studies and randomized trials have investigated the effects of maternal DHA consumption on neurodevelopment, with heterogeneity in assessed outcomes (visual acuity, global cognition, specific neurologic domains) and timing of DHA intake (gestational vs. nursing). While dose responses and specific effects require further investigation, the studies examined together indicate that maternal intake of DHA is beneficial for early neurodevelopment.
- Risks of mercury-methylmercury and neurodevelopment
    - Among children from the Faroe Islands, New Zealand and Poland, higher gestational exposure to mercury was associated with lower scores on some neurologic tests (e.g., finger tapping, naming tests), but not others. In contrast, higher gestational exposure to mercury was associated with higher scores on some neurologic tests among Seychellois children
    - Randomized trials to test effects of reducing low-level methylmercury exposure during gestation have not been performed. But, given associations with some lower neurologic test scores in some studies, and clinical neurotoxicity of methylmercury following high-level accidental exposures, authors note that it is prudent to conclude that subclinical neurodevelopmental deficits may occur at lower exposure levels
- Health effects of methylmercury in adults
    - Cardiovascular disease: Several studies have evaluated the relationship between mercury exposure and incidence of cardiovascular disease and have shown conflicting

results that provide inconclusive evidence for cardiovascular toxicity of mercury
    - Neurologic outcomes: It is unclear whether low-level methylmercury affects subclinical neurologic outcomes in adults and, if so, what quantities or durations of exposure are necessary. Conversely, a growing body of evidence suggests that fish consumption may favorably affect clinical neurologic outcomes in adults, including ischemic stroke, cognitive decline and dementia and depression and other neuropsychiatric disorders
- Risks of PCBs and dioxins: Cancer risks
    - Evaluated age-specific estimates, based on allocation of lifetime cancer risks (adjusted for competing risks) by age-specific cancer mortality and 25% reduction in age-specific CHD mortality and found that, for all ages evaluated (25 to 34 to 85 or more years), CHD benefits outweighed cancer risks by 100- to 370-fold for farmed salmon and by 300- to more than 1,000-fold for wild salmon
    - Prospective studies in humans have seen little evidence for effects of fish intake on cancer risk.

Author Conclusion:

- For major health outcomes among adults, based on both the strength of the evidence and the potential magnitudes of effect, the benefits of fish intake exceed the potential risks
- For women of childbearing age, benefits of modest fish intake, excepting a few selected species, also outweigh risks
- Women of childbearing age and nursing mothers should consume two seafood servings per week, limiting intake of selected species. A variety of seafood should be consumed; individuals with very high consumption (five or more servings per week) should limit intake of species highest in mercury levels
- Levels of dioxins and polychlorinated biphenyls in fish are low, and potential carcinogenic and other effects are outweighed by potential benefits of fish intake and should have little impact on choices or consumption of seafood (women of childbearing age should consult regional advisories for locally caught freshwater fish).

Reviewer Comments:

- *Article does not describe:*
    - *Start date for range of articles searched*
    - *Appraisal of the quality and validity of studies included in the review*
    - *Explicit number of initial or final articles included for each focused question asked*
- *Per authors:*
    - *Regarding evidence on methylmercury and development, comparisons across studies are limited by heterogeneity of study designs (prospective vs. cross-sectional), mercury assessment methods, neurologic tests used, timing of assessment (infancy vs. childhood) and statistical methods. Some analyses are also limited by multiple statistical testing or incomplete adjustment for other potential risk factors. Randomized trials to test effects of reducing low-level methylmercury exposure during gestation have not been performed*
    - *Studies involving estimated cancer risks include are based on animal-experimental data and limited studies in humans at high doses.*

Research Design and Implementation Criteria Checklist: Review Articles

Relevance Questions		
1.	Will the answer if true, have a direct bearing on the health of patients?	Yes
2.	Is the outcome or topic something that patients/clients/population groups would care about?	Yes
3.	Is the problem addressed in the review one that is relevant to nutrition or dietetics practice?	Yes
4.	Will the information, if true, require a change in practice?	Yes

Validity Questions		
1.	Was the question for the review clearly focused and appropriate?	Yes
2.	Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search termsused described?	Yes
3.	Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?	Yes
4.	Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible?	Yes
5.	Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?	???
6.	Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?	Yes
7.	Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described?	Yes
8.	Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?	Yes
9.	Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?	Yes
10.	Was bias due to the review's funding or sponsorship unlikely?	Yes